Tobacco Smoking and Colorectal Hyperplastic and Adenomatous Polyps

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Abstract

Colorectal adenomas and possibly some hyperplastic polyps are precursors of colorectal cancer. Tobacco use is associated in epidemiologic studies with these polyps, although links between smoking and colorectal cancer are less consistent. To characterize the role of tobacco in early colorectal carcinogenesis, we compared tobacco use among 4,383 subjects with histologically verified benign (hyperplastic or adenomatous) polyps of the distal colon (descending colon, sigmoid, and rectum) with tobacco use among 33,667 subjects who were endoscopy negative for distal colon tumors, in the screening arm of the Prostate, Lung, Colorectal, and Ovarian Trial, a randomized trial of flexible sigmoidoscopy. Risks, estimated by the odds ratio (OR), associated with current cigarette use were OR = 4.4 [95% confidence interval (95% CI), 3.7-5.2] for hyperplastic polyps only, OR = 1.8 (95% CI, 1.5-2.1) for adenomas only, and OR = 6.2 (95% CI, 4.7-8.3) for subjects with both hyperplastic and adenomatous polyps concurrently. Effects were weaker among ex smokers; the smoking-associated ORs remained consistently higher for hyperplastic polyps. This pattern was also seen in relation to cigarettes smoked per day, smoking duration, and pack-years. Tobacco-associated risks for multiple polyps were also stronger when hyperplastic disease was involved. In conclusion, tobacco use, particularly recent use, increases risk for both adenomatous and hyperplastic polyps, but the risks are substantially greater for hyperplastic lesions. (Cancer Epidemiol Biomarkers Prev 2006;15(5):897–901)

Introduction

Colorectal adenoma is a recognized precursor for colorectal cancer. Hyperplastic polyps of the colorectal are generally thought not to lead to malignancy, although a subset of these lesions may have malignant potential (1-5).

Tobacco use has been linked to increased risk for colorectal adenoma in many epidemiologic studies (6) and to colorectal cancer, at least among long-term smokers (7, 8). Morimoto et al. (9), studying 794 subjects with colon polyps identified at colonoscopy clinics, reported that tobacco use was strongly associated with hyperplastic polyps, and that the observed tobacco-adenoma association was largely restricted to cases with concomitant hyperplastic polyps, and suggested to the authors that the tobacco-adenoma relationship per se may be spurious or that the hyperplastic-adenoma combination may define a particular risk phenotype.

To better characterize the association between tobacco use and colorectal polyps, we studied >4,000 cases with left-sided polyps (adenoma or hyperplastic polyp) identified among >56,000 participants in a National Cancer Institute randomized control trial of flexible sigmoidoscopy for the early detection of colorectal cancer.

Materials and Methods

This study was carried out among participants randomized to the screening arm of the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (10), a multisite investigation (Birmingham, AL; Denver, CO; Detroit, MI; Honolulu, HI; Marshfield, WI; Minneapolis, MN; Pittsburgh, PA; Salt Lake City, UT; St. Louis, MO; and Washington, DC) of the effectiveness of early detection for these cancers. Subjects randomized to the screening arm of the trial have flexible sigmoidoscopic examination of the distal colon (60 cm) at study entry. Screenees with lesions suspect for colorectal neoplasia (i.e., sigmoidoscopically visualized polyploid lesion or mass) are referred for endoscopic follow-up, including histopathologic exam. The Prostate, Lung, Colorectal, and Ovarian Trial obtained all available medical-pathologic reports on all lesions removed during the diagnostic colonoscopy and related surgical procedures. This information was abstracted and coded by trained medical abstractors. Questionnaire data and biological samples are also collected from trial participants for etiologic substudies (11). Study participants provided informed consent, following approval by the institutional review boards of the National Cancer Institute and the 10 screening centers.

Between September 1993 and September 2000, a total of 56,173 participants (men and women, ages 55-74 years) had successful sigmoidoscopic exams (insertion to at least 50 cm with >90% of mucosa visible or a suspect lesion found). Of these screening arm participants, 56,079 (99.8%) completed a baseline risk factor questionnaire. We investigated 38,050 subjects, after excluding 18,029 participants for the following reasons: (*a*) previous history of cancer, except basal cell skin cancer; (*b*) self-reported history of ulcerative colitis, Crohn's disease, familial polyposis, colorectal polyps, or Gardner's syndrome; and (*c*) missing or inadequate information on food intake. Some participants were excluded for more than one reason.

We focused on the distal colon (including the descending and sigmoid colon and the rectum) because the screening examination covered only the distal colon. Of the 38,050 participants, 33,667 had no distal lesions suspicious for neoplasia. These participants formed the control group and were compared with 4,383 cases with pathologically verified polyps of the distal colon, including 1,545 cases with

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hyperplastic polyps (only), 2,339 cases with adenoma (only), and 499 cases with both hyperplastic polyps and adenoma. Participants were ineligible for this study if they had colorectal lesions (polyps or cancer) of unknown location, polyps of uncertain histology or cancer, indeterminate screening results, or a suspect screening result but no follow-up endoscopy. The update of data was through January, 2003.

Information on tobacco use, medical history, reproductive history (women), use of aspirin or aspirin-containing products and ibuprofen-containing products, family history of cancer, demographic information, and dietary history was collected at the baseline interview. The smoking questions were as follows: ''Have you ever smoked cigarettes regularly for 6 months or longer?'' if yes, we asked, ''At what age did you start smoking cigarettes regularly?''; ''Do you smoke cigarettes regularly now?''; ''During periods when you smoked, how many cigarettes did or do you smoke per day?'' If subjects stopped smoking, we asked, ''At what age did you last stop smoking cigarettes regularly?'' In addition, we also asked if subjects smoked pipes or cigars, and how often they smoked filter or nonfilter cigarettes. We calculated pack-years from number of packs of cigarettes smoked per day and interval years between age started and age stopped (or age at interview for current smokers). Subjects who smoked cigarettes regularly for ≥6 months were classified as current smokers; Subjects who answered ''No'' to the question if he or she smoked cigarettes regularly now were classified as ex smokers; subjects who never smoked cigarettes, pipes, or cigars were classified as never smokers.

Odds ratios and 95% confidence intervals were calculated by multiple logistic regressions (12). Trend tests were assessed using an ordinal score for each categorical variable. The base model included age and center. We then included other factors that changed the base odds ratio for ever smoking by ≥10%, which included sex, education, fruit intake, and alcohol consumption. Further adjustment for family history of colorectal cancer, marital status, body mass index, physical activity (hours/wk), red meat intake, dietary intake of fiber, calcium, and folate, and aspirin/ibuprofen use did not change the smoking associations with polyps; thus, these variables were not included in the final models. Polytomous regression was applied to test risk differences among the three categories of polyps (hyperplastic only, adenoma only, and both types concurrently).

Results

Among controls, never, current, and former smokers differed little with respect to age, race, and body mass index (Table 1). Smoking was more common among men than women. Fewer current smokers were married, and current smokers tended to have lower educational attainment, lower physical activity, greater alcohol and meat consumption, and lower fruit consumption. Former and current smokers were similar with respect to age started smoking and usual amount smoked. Current smokers used tobacco longer and consequently had greater total exposure (pack-years).

Ever use of cigarettes was associated with increased risk of hyperplastic polyps (odds ratio, 2.1; 95% confidence interval, 1.9-2.4), adenomatous polyps (odds ratio, 1.2; 95% confidence interval, 1.1-2.3), and both adenomatous and hyperplastic polyps (odds ratio, 2.3; 95% confidence interval, 1.9-2.9; Table 2). Compared with never smokers, current smokers had 4-fold increase in risk, and former smokers only had 2-fold increase in risk. Risks increased with increasing numbers of cigarettes usually smoked, duration of cigarette use, and pack-years of use. Under each tobacco use scenario, risks were greatest for hyperplastic polyps; however, dose-response trends for adenoma were also highly statistically significant.

Examining dose metrics (cigarettes per day, duration, and pack-years) and recency of tobacco use (Table 3), subjects who quit smoking at least 20 years before study showed modest excess risks only for the heaviest users of tobacco (for adenoma, pack-years ≥40 and for hyperplastic polyps, >20 cigarettes per day or ≥30 pack-years). Subjects who quit smoking 10 to 19 years ago and particularly those who smoked more recently (current smokers and quit <10 years ago) showed dose-response relationships for hyperplastic polyps and adenoma, with the strongest associations for hyperplastic polyps. Polytomous regression analyses confirmed significant differences in risk for hyperplastic and adenomatous polyps, with respect to recency of use and smoking dose ($P < 0.001$). Cross-tabulations of risk associated with duration of tobacco use and recency also indicated that recency was a more important determinant than duration (Table 3).

Tobacco-associated risks among current and ex smokers tended to be stronger for multiple and large adenomatous and hyperplastic polyps, with no clear differentials seen by tumor histology or location (Table 4). Further examination of subjects

Table 1. Characteristics of smoking variables and other risk factors by never, former, and current smoking among controls (Prostate, Lung, Colorectal, and Ovarian Trial, 1993-2000)

	Never smokers (N = 15,498)	Current smokers (N = 2,394)	Former smokers (N = 14,157)
Age	62.9 (5.3)	61.3 (4.7)	62.7 (5.2)
Sex (% men)	36.7	56.9	61.7
Education (%)			
<12 y	5.0	10.7	6.8
12 y/high school equivalent	36.7	39.1	35.1
Some college	19.3	24.0	22.3
College and above	39.0	26.2	35.8
Race (% White)	90.5	87.7	90.6
Marital status (% married/as married)	80.1	67.2	80.6
Ever use aspirin or ibuprofen (%)	55.7	63.3	63.7
Physical activity >3 h/wk (%)	41.7	26.3	41.7
Body mass index (kg/m^2)	27.0 (4.9)	26.2 (4.5)	27.6 (4.7)
Alcohol intake (g/d)	5.6 (13.4)	16.8 (35.0)	13.9 (25.7)
Fruit intake (g/d)	3.7 (2.3)	2.5 (2.0)	3.3 (2.2)
Red meat (g/d)	66.8 (56.4)	98.8 (73.7)	81.4 (67.6)
Smoking rates (%)	—	7.5	44.2
Age started smoking	—	19.2 (6.5)	18.5 (4.5)
Years since started smoking	—	42.1 (7.8)	44.3 (6.6)
Cigarettes smoked per day	—	18.4 (10.9)	18.2 (12.2)
Smoking duration (y)	—	41.6 (7.8)	22.2 (12.1)
Pack-years	—	39.1 (24.9)	22.0 (20.8)

NOTE: Unless otherwise specified, means (SD) are presented.

Table 2. Odds ratios and 95% confidence intervals of tobacco use for polyps of the distal colon and rectum (Prostate, Lung, Colorectal, and Ovarian Trial, 1993-2000)

Tobacco use	No. controls	Hyperplatic polyps only		Adenomas only		Concurrent hyperplastic polyps and adenomas	
		No. cases	OR (95% CI)	No. cases	OR (95% CI)	No. cases	OR (95% CI)
Smoking status							
Never smoked	15,010	444		882		106	
Ever cigarette smokers	15,838	1,040	2.1 (1.9-2.4)	1,343	1.2 (1.1-1.3)	364	2.3 (1.9-2.9)
Current cigarette smokers	2,253	278	4.4 (3.7-5.2)	275	1.8 (1.5-2.1)	112	6.2 (4.7-8.3)
Ex cigarette smokers	13,585	762	1.8 (1.6-2.1)	1,068	1.1 (1.0-1.2)	252	2.2 (1.7-2.8)
Ex cigarette, current cigar/pipe users*	341	26	2.4 (1.5-3.6)	28	1.0 (0.7-1.5)	15	4.4 (2.5-7.9)
Never cigarette but current cigar/pipe users*	249	6	0.7 (0.3-1.6)	22	1.1 (0.7-1.7)	4	1.6 (0.6-4.5)
Never cigarette but ex cigar/pipe users*	1,147	54	1.4 (1.0-1.9)	85	0.9 (0.7-1.2)	23	2.0 (1.3-3.2)
Cigarettes smoked per day							
1-10	4,263	195	1.6 (1.3-1.9)	296	1.1 (1.0-1.3)	63	2.0 (1.5-2.8)
11-20	5,898	386	2.2 (1.9-2.5)	496	1.2 (1.1-1.3)	142	2.8 (2.2-3.7)
21-30	3,017	245	2.7 (2.3-3.2)	286	1.3 (1.1-1.5)	89	3.4 (2.5-4.6)
≥31	2,636	213	2.6 (2.2-3.1)	263	1.3 (1.1-1.5)	70	2.9 (2.1-4.0)
P_{trend}			<0.0001		0.04		0.05
Smoking duration (y)							
<15	4,093	147	1.2 (1.0-1.4)	258	1.0 (0.8-1.1)	38	1.2 (0.8-1.7)
15-24	3,710	156	1.4 (1.1-1.7)	262	1.0 (0.9-1.2)	57	1.8 (1.3-2.5)
25-34	3,273	237	2.4 (2.1-2.9)	280	1.2 (1.1-1.4)	69	2.6 (1.9-3.5)
35-44	3,281	333	3.5 (3.0-4.1)	341	1.5 (1.3-1.7)	115	4.3 (3.3-5.7)
≥45+	1,161	152	4.2 (3.4-5.1)	178	1.8 (1.5-2.2)	79	7.2 (5.2-10.0)
P_{trend}			<0.0001		<0.0001		<0.0001
Pack-years							
1-9	5,075	204	1.4 (1.2-1.6)	322	1.0 (0.9-1.2)	58	1.5 (1.1-2.1)
10-19	2,953	149	1.7 (1.4-2.0)	239	1.1 (1.0-1.3)	48	1.9 (1.4-2.8)
20-29	2,434	161	2.3 (1.9-2.8)	187	1.1 (0.9-1.3)	56	2.8 (2.0-4.0)
30-39	1,850	177	3.2 (2.6-3.8)	193	1.4 (1.2-1.7)	77	4.7 (3.5-6.5)
40-54	1,444	145	3.5 (2.9-4.3)	156	1.5 (1.3-1.8)	44	3.7 (2.5-5.3)
≥55	1,573	173	3.7 (3.0-4.5)	200	1.6 (1.4-1.9)	69	4.8 (3.4-6.6)
P_{trend}			<0.0001		<0.0001		<0.0001
Years since stopped smoking (y)							
≥40	832	34	1.2 (0.8-1.7)	65	1.0 (0.7-1.3)	11	1.3 (0.7-2.4)
30-<40	3,016	121	1.3 (1.0-1.6)	200	0.9 (0.8-1.1)	32	1.2 (0.8-1.8)
20-<30	3,680	149	1.3 (1.1-1.6)	260	1.0 (0.9-1.2)	48	1.5 (1.1-2.2)
10-<20	3,390	216	2.2 (1.8-2.6)	287	1.2 (1.1-1.4)	71	2.6 (1.9-3.5)
<10	2,455	235	3.3 (2.8-3.9)	238	1.4 (1.2-1.7)	85	4.4 (3.2-5.9)
P_{trend}			<0.0001		<0.0001		<0.0001

NOTE: ORs adjusted for age, sex, education, fruit, alcohol intake, and study centers. P_{trends} presented were estimated by using logistic regression among ever smokers only.

Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval.

*ORs for cigar/pipe use were estimated among men only.

with both adenomatous and hyperplastic polyps showed that smoking was a risk factor for tumor multiplicity of both polyp types (data not shown). The risk patterns were similar between men and women; thus, the gender-specific results were not presented.

Discussion

Our study showed that tobacco use is a risk factor for adenomatous and hyperplastic polyps of the distal colon. Risks were substantially greater for hyperplastic lesions, although independent risks for adenoma were also found. We found that current and recent smoking was strongly associated with polyps, consistent with our previous observations that tobacco metabolism-related genetic variants were strongly tied to advanced adenoma risk in recent smokers (13-16). Clear risk differentials by tumor location (sigmoid and descending colon versus rectum) were not observed.

Tobacco use has been associated with about 2- to 5-fold risks for adenoma compared with nonsmokers in many epidemiologic studies (6). Several investigators pointed to duration of tobacco use as a key determinant of adenoma risk (17-21). In our detailed analysis of duration and recency of use, we found that recency strongly predicted risk level, whereas duration of use, among people who quit smoking at least 10 years, was only weakly associated with risk. This observation may parallel the natural history of polyp development, suggesting that the most recent decade is the relevant time frame for the development of these tobacco-related premalignant tumors.

Although hyperplastic polyps have historically been considered unrelated to colon carcinogenesis, molecular changes consistent with neoplasia can occur in hyperplastic polyps, including hypomethylation of the *c-myc* gene, high levels of microsatellite instability, and *ras* mutations (2, 22-27). Cigarette smoking has also been positively associated with microsatellite instability in colorectal cancer in two epidemiologic studies (28, 29). Our finding of greater tobacco-associated risks for hyperplastic than adenomatous polyps is consistent with reports by Morimoto et al. (9) and Potter et al. (30). Because most studies did not describe risks associated with adenoma alone versus adenoma concurrent with hyperplastic polyps, prior estimates of tobacco-associated risks for adenoma per se may have been overestimated. Our data suggest that adenoma risks increase to about only 2-fold in recent smokers with heavy use patterns. Nevertheless, the smoking risk pattern for the cases with concurrent hyperplastic polyps and adenomas may involve more complex mechanisms, and further studies are required.

Because of the large size of this study, we were able to relate tobacco use patterns to specific polyp subtypes, showing that tobacco use was most strongly associated with tumor multiplicity for both hyperplastic and adenomatous polyps, rather than to tumor size or histologic structure, possibly indicating that tobacco-related exposures affect the early development of polyps and have less influence on their progression to larger size or more advanced histologic type. If tobacco use preferentially effects early tumor development, this may explain the generally weak association between smoking and colorectal cancer, except among those who smoked many decades in the past (8). This hypothesis could be evaluated by examining risk for cancer related to tobacco exposure in the past, irrespective of duration or current use. From a prevention standpoint, these results suggest that colorectal cancer screening coupled with smoking cessation may have the potential to yield an initial and a long-term decrease in colorectal cancer risk.

The mechanisms by which cigarette smoking causes colorectal tumors are still under study; however, there is ample evidence that tobacco combustion products are carcinogenic, with colonic tissue being a potential site of action (31). Further study of the underlying biology of tobacco-related hyperplastic versus adenomatous lesions will help to elucidate this process.

Our study focused on prevalent polyps at the entry screening exam in the Prostate, Lung, Colorectal, and Ovarian Trial. To some extent, the risk associations observed, particularly for adenoma, are correlated with transition times in the preneoplastic state, rather than underlying incidence of

Table 3. Odds ratios and 95% confidence intervals in relation to the combined effects of years since stopped smoking and smoking doses for hyperplastic polyps and adenomas of the distal colon and rectum (Prostate, Lung, Colorectal, and Ovarian Trial, 1993-2000)

	Years since quit						P_{trend}*
	≥20		10 to <20		0 to <10		
	Cases	OR (95% CI)	Cases	OR (95% CI)	Cases	OR (95% CI)	
Hyperplastic polyps only							
Cigarettes smoked per day							
1-10	88	1.2 (0.9-1.5)	34	1.7 (1.2-2.5)	72	2.6 (2.0-3.3)	<0.0001
11-20	111	1.2 (1.0-1.5)	65	1.9 (1.4-2.5)	208	4.0 (3.3-4.8)	<0.0001
≥21	104	1.5 (1.2-1.8)	117	2.6 (2.1-3.2)	233	4.5 (3.8-5.4)	<0.0001
P_{trend}*		0.42		0.03		0.0001	
Duration (y)							
<25	250	1.2 (1.0-1.4)	41	1.8 (1.3-2.5)	12	2.2 (1.2-4.0)	0.001
25 to <35	50	2.0 (1.4-2.7)	117	2.2 (1.8-2.8)	70	3.5 (2.7-4.6)	0.03
≥35	1	0.8 (0.1-6.4)	56	2.4 (1.7-3.2)	428	4.0 (3.4-4.6)	0.002
P_{trend}*		0.02		0.14		0.01	
Pack-years							
<30	254	1.2 (1.1-1.5)	101	1.8 (1.5-2.3)	159	3.2 (2.6-3.8)	<0.0001
30 to <40	22	1.6 (1.0-2.6)	36	2.9 (2.0-4.2)	119	3.8 (3.1-4.8)	0.005
≥40	19	1.6 (1.0-2.5)	72	2.4 (1.9-3.2)	227	4.7 (3.9-5.6)	<0.0001
P_{trend}*		0.41		0.08		0.0001	
Adenomas only							
Cigarettes smoked per day							
1-10	156	1.0 (0.8-1.2)	45	1.1 (0.8-1.4)	88	1.4 (1.1-1.8)	0.007
11-20	191	0.9 (0.8-1.1)	97	1.2 (1.0-1.5)	204	1.7 (1.4-2.0)	<0.0001
≥21	177	1.0 (0.9-1.2)	145	1.3 (1.1-1.6)	220	1.7 (1.4-2.0)	<0.0001
P_{trend}*		0.91		0.10		0.32	
Duration (y)							
<25	442	1.0 (0.8-1.1)	60	1.2 (0.9-1.6)	18	1.6 (1.0-2.6)	0.001
25 to <35	74	1.1 (0.9-1.5)	152	1.3 (1.1-1.5)	54	1.3 (0.9-1.7)	0.28
≥35	4	1.4 (0.5-3.9)	74	1.2 (0.9-1.5)	441	1.7 (1.5-1.9)	0.007
P_{trend}*		0.06		0.16		0.37	
Pack-years							
<30	445	1.0 (0.8-1.1)	143	1.1 (1.0-1.4)	160	1.4 (1.2-1.7)	<0.0001
30 to <40	25	0.8 (0.5-1.2)	42	1.4 (1.0-1.9)	126	1.7 (1.4-2.1)	0.001
≥40	43	1.4 (1.0-2.0)	93	1.3 (1.0-1.6)	220	1.8 (1.5-2.1)	0.06
P_{trend}*		0.09		0.16		0.20	
Concurrent hyperplastic polyps and adenomas							
Cigarettes smoked per day							
1-10	23	1.3 (0.8-2.0)	15	3.1 (1.8-5.3)	22	3.1 (1.9-5.0)	0.002
11-20	31	1.2 (0.8-1.8)	21	2.2 (1.4-3.6)	88	6.1 (4.5-8.2)	<0.0001
≥21	37	1.8 (1.2-2.6)	35	2.7 (1.8-4.0)	87	5.8 (4.2-7.9)	<0.0001
P_{trend}*		0.30		0.82		0.05	
Duration (y)							
<25	77	1.4 (1.0-1.8)	13	2.3 (1.3-4.2)	5	3.7 (1.5-9.2)	0.01
25 to <35	14	1.8 (1.0-3.0)	34	2.3 (1.6-3.5)	21	4.4 (2.7-7.2)	0.01
≥35	0	—	24	3.3 (2.0-5.2)	170	5.5 (4.2-7.2)	0.02
P_{trend}*		0.51		0.51		0.19	
Pack-years							
<30	75	1.3 (1.0-1.8)	34	2.3 (1.6-3.5)	53	4.2 (3.0-5.9)	<0.0001
30 to <40	11	2.7 (1.4-5.1)	10	2.9 (1.5-5.6)	56	6.2 (4.4-8.8)	<0.0001
≥40	4	1.1 (0.4-2.9)	24	2.7 (1.7-4.3)	85	5.9 (4.3-8.0)	<0.0001
P_{trend}*		0.76		0.62		0.09	

NOTE: ORs compared with never tobacco users and adjusted for age, sex, education, fruit, alcohol intake, and study centers.
Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval.
*Dose-response trends were tested by using logistic regression among ever smokers only.

Table 4. Odds ratios and 95% confidence intervals of cigarette smoking for hyperplastic and adenomatous polyps of the distal colon and rectum by morphological characteristics and subsite of the descending colon, sigmoid colon, and rectum (Prostate, Lung, Colorectal, and Ovarian Trial, 1993-2000)

	Ex smokers				Current smokers			
	Hyperplastic polyps		Adenomatous polyps		Hyperplastic polyps		Adenomatous polyps	
	Cases	OR (95% CI)	Cases	OR (95% CI)	Cases	OR (95% CI)	Cases	OR (95% CI)
Single/multiple								
Single	472	1.6 (1.4-1.9)	771	1.1 (1.0-1.2)	153	3.3 (2.7-4.1)	190	1.6 (1.3-1.9)
Multiple	290	2.3 (1.9-2.9)	297	1.2 (1.0-1.5)	125	6.2 (4.7-8.0)	85	2.2 (1.7-2.9)
Size (cm in diameter)								
Small (<1 cm)	547	1.6 (1.4-1.9)	636	1.0 (0.9-1.2)	179	3.3 (2.7-4.0)	151	1.5 (1.3-1.9)
Large (≥1 cm)	45	2.3 (1.3-4.1)	327	1.2 (1.0-1.5)	13	4.0 (1.9-8.5)	91	2.0 (1.5-2.5)
Villous								
No			834	1.1 (1.0-1.2)			222	1.8 (1.5-2.1)
Yes			234	1.2 (0.9-1.4)			53	1.5 (1.1-2.1)
Subsite of distal colorectum*								
Descending and sigmoid colon	491	1.7 (1.5-2.0)	854	1.1 (1.0-1.3)	208	4.6 (3.8-5.6)	232	1.9 (1.6-2.2)
Rectum	350	2.1 (1.7-2.5)	304	1.1 (0.9-1.3)	112	4.2 (3.2-5.4)	72	1.5 (1.2-2.0)

NOTE: ORs compared with never tobacco users and adjusted for age, sex, education, fruit, alcohol intake, cigarettes smoked per day, and study centers.
Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval.
*Adenomas with multiple sites of the descending colon, sigmoid colon, and rectum were not included.

disease. We lack detailed knowledge of the natural history of polyps, but further study of incident polyps among subjects who initially screened negative in the Prostate, Lung, Colorectal, and Ovarian Trial is proceeding. This may permit further analysis of the association of smoking characteristics on near term development of colonic polyps.

In conclusion, tobacco use was associated with increased prevalence of polyps of the distal colon in subjects screened by sigmoidoscopy in the Prostate, Lung, Colorectal, and Ovarian Trial. The associations were mostly correlated with recent tobacco use and were stronger for hyperplastic than for adenomatous polyps.

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